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## Two subdomains of negative symptoms in psychotic disorders

Genetic Risk and Outcome of Psychosis Investigators

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## Two subdomains of negative symptoms in psychotic disorders: Established and confirmed in two large cohorts

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### ABSTRACT

Negative symptoms of schizophrenia are normally grouped into a single category. However, the diversity of such symptoms suggests that they are actually made up of more than one dimension. The DSM-V proposes two negative symptom domains, namely expressive deficits and avolition/asociality. We investigated whether the negative symptoms do indeed have two dimensions. An exploratory factor analysis was carried out based on interviews with the PANSS (664 patients). We restricted our analysis to items that had been described as negative symptoms in previous factor analyses. The symptom structure was then tested for stability by performing a confirmatory factor analysis on PANSS interviews from a separate cohort (2172 patients). Exploratory factor analysis yielded a two-factor structure of negative symptoms. The first factor consisted of PANSS items Flat affect, Poor rapport, Lack of spontaneity, Mannerisms and posturing, Motor retardation, and Avolition. The second factor consisted of Emotional withdrawal, Passive/apathetic social withdrawal, and Active social avoidance. The first factor could be related to expressive deficits, reflecting a loss of initiative, and the second factor to social amotivation, related to community interaction. This factor structure supports the DSM-V classification and may be relevant for pathophysiology and treatment of schizophrenia and other psychotic disorders.

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### 1. Introduction

The symptoms of schizophrenia and other psychotic disorders are often categorized into three main domains: positive symptoms, negative symptoms, and cognitive impairments (American Psychiatric Association, 2000; Mueser and McGurk, 2004). Negative symptoms have been defined as an absence of normal behaviors,

including flattened emotional response, poverty of speech, lack of initiative, lack of pleasure and social withdrawal (Andreasen and Flaum, 1991). They are difficult to treat and are an important predictor for poor social outcome in schizophrenia (Pinkham et al., 2003).

The current DSM-IV considers negative symptoms as one dimension. However, instruments like the Scale for Assessment of Negative Symptoms (SANS) or the Positive and Negative Syndrome Scale (PANSS) show considerable heterogeneity in items measuring negative symptoms (Andreasen, 1983; Kay et al., 1987). This wide range of symptoms, hitherto classified as one group, may in fact reflect different subgroups, with each a different neural, social, or psychological etiology (Keefe et al., 1992). The new DSM-V proposes a two-subdomain model of negative symptoms, with one domain related to expressive deficits including affective, linguistic

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and paralinguistic expressions, and the second domain related to avolition for social activities (Kirkpatrick and Fischer, 2006; Messinger et al., 2011). Such a classification with two subgroups could have important implications for research, diagnostics and treatment (Blanchard and Cohen, 2006; Messinger et al., 2011).

Negative symptoms have always been the 'pièce de résistance' in treatment. Recently some evidence is emerging that treatment with modafinil may have beneficial effects on negative symptoms (Arbabi et al., 2011), mainly restricted to the anhedonia-asociality item of the SANS (Bobo et al., 2011). Cognitive behavioral therapy is reported to be effective in improving motivation, apathy and social participation (Grant et al., 2011). Thus, these treatments may address different biological and psychological issues of the group of negative symptoms. Instruments that reliably distinguish these two distinct subgroups of symptoms could be supportive for the research into treatment strategies aimed at negative symptoms.

One way to investigate whether negative symptoms comprise more than one symptom domain is to assess the correlational structure of the measures by factor analysis (Blanchard and Cohen, 2006; Stevens, 1996; Tabachnik and Fidell, 2007). Factor analyses have already established that negative symptoms comprise a separate domain within the full symptom range seen in schizophrenia and related psychotic disorders (Blanchard and Cohen, 2006; Van der Gaag et al., 2006a,b). However, the concept of negative symptoms is still heterogeneous, and previous studies with factor analysis have shown that there may be two (or three) subdomains (Blanchard and Cohen, 2006; Kirkpatrick and Fischer, 2006; Kirkpatrick et al., 2006; Peralta and Cuesta, 1995).

Although negative symptoms often constitute one factor in factor analysis of the whole PANSS (Van der Gaag et al., 2006a,b), this negative symptom factor appears to be unstable or sometimes even split (Blanchard and Cohen, 2006; Lindström and Von Knorring, 1993; Van den Oord et al., 2006). In factor analysis the number of factors is often predefined or based on variance measures. When the number of factors is set too low, this could force all negative symptoms in one factor, while they should actually constitute multiple factors (Blanchard and Cohen, 2006).

The aim of this study is to increase generalizability of earlier findings reporting on two sub-domains of negative symptoms. So far, most studies on the structure of negative symptoms have used the Scale for Assessment of Negative Symptoms (SANS) (Andreasen, 1983). Since inferences based on one symptom scale are limited (Blanchard and Cohen, 2006; Horan et al., 2006), replication with the Positive and Negative Syndrome Scale (PANSS) – a widely used instrument (Foussias and Remington, 2010) – could increase the construct validity. The PANSS and the SANS have a considerable overlap in how they measure symptoms, but the specific set of symptoms they measure differs (Lyne et al., 2012; Rabany et al., 2011), which makes the PANSS an interesting addition to factor analysis findings on the SANS. In addition, most previous factor analyses were performed on relatively small samples ( $n < 200$ ) and only on patients with a diagnosis of schizophrenia and substantially evident negative symptoms.

The aim of this study is to examine the negative symptom structure and its resemblance to the model proposed by the DSM-V while taking care of aforementioned limitations of earlier studies. Therefore, we investigated negative symptom structure in large, unbiased (i.e. not selected for a certain research purpose) groups of patients with a broad range of psychotic disorders using the PANSS to validate findings on the SANS. We focus on PANSS items already related to negative symptoms. Exploratory factor analysis (EFA) will be applied to reveal the underlying structure of the symptoms, and confirmatory factor analysis (CFA) will be performed in a separate, large sample to determine the robustness of the factor structure (Blanchard and Cohen, 2006).

## 2. Methods

### 2.1. Study samples

All data used in this study were handled anonymously, and all subjects gave oral and written informed consent. Research was carried out in accordance with the latest version of the Declaration of Helsinki and approved by the local ethical committee. Most patients in the study samples were outpatient, recently diagnosed with a psychotic disorder (American Psychiatric Association, 2000). A definite diagnosis could not always been given at this point, because of the often short duration of illness.

For the EFA, a cohort of 664 cases from the province of Groningen (Early Psychosis Outcome Groningen, EPOG), the Netherlands, was used. These patients followed a clinical assessment for diagnostic purposes at the department of psychotic disorders in the University Center Psychiatry in Groningen (1998–2009). All patients had a diagnosis in the psychotic spectrum according to DSM-IV diagnostic criteria.

For the CFA, we used an independent sample of 2172 cases, comprising three subsamples. The first group comprised a nationwide, longitudinal study: Genetic Risk and Outcome of Psychosis (GROUP) of persons aged 18–50 years, Dutch speaking and on stable antipsychotic treatment ( $>1$  month) (2004–2007). They all had a diagnosis of non-affective psychotic disorder (schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, psychotic disorder NOS; DSM-IV). The second group consisted of subjects with a first episode of psychosis and treated at the Academic Medical Centre, Amsterdam (2006–2010). The third group was a cohort from the University Medical Center Utrecht, the Netherlands, who underwent a PANSS interview for clinical or research purposes (2006–2011).

The demographic variables are presented per cohort to provide a general overview of the samples (Table 1). Given that the data were collected for diagnostic purposes in the first place, not all demographic information was fully available. Diagnoses were combined in categories for overview (the category psychotic disorders included psychotic disorder NOS, brief psychotic disorder, and delusional disorder). Age and PANSS scores (not normally distributed) were tested with a Kruskal Wallis test between all samples and with a Mann–Whitney  $U$  test between the EFA and CFA cohorts. Gender and primary diagnosis were tested with a Chi-squared test for independence both between all samples and the EFA and CFA samples.

### 2.2. Study design

The PANSS is a diagnostic interview with three parts: Positive symptoms (7 items), Negative symptoms (7 items) and General pathology (16 items) (Kay et al., 1987). The interviews were administered by experienced raters who had, at minimum, participated in an annual consensus training (inter-rater reliability  $> 0.8$ ).

We choose to do a data-driven, non-biased selection of items that reflect negative symptoms in the PANSS. To accomplish this, we selected items that had been identified as negative symptoms in factor analyses of the whole PANSS, and that also showed a moderate correlation with other negative symptoms (For correlation matrix see Supplementary material). To identify items of previous factor analyses, a literature search was conducted in PubMed using the search terms: "factor analysis OR factor structure AND PANSS". All retrieved studies were searched for cross-references: 33 studies that reported on a negative symptom factor in the PANSS were identified (Bell et al., 1992, 1994; Davis and Chen, 2001; Dollfus and Petit, 1995a,b; Drake et al., 2003; Emsley et al., 2003; Fitzgerald

**Table 1**  
Overview of the cohorts' demographic data; the EPOG cohort was used for the exploratory factor analysis (EFA), the GROUP cohort and the Utrecht (UTR) and Amsterdam (AMS) cohorts were combined for the confirmatory factor analysis (CFA); '–' indicates data was not available, some percentages do not reach 100% because only part of the data was available for these categories; 'X' indicates that a category was not present for that particular dataset.

		EFA		CFA	
		EPOG	GROUP	AMS	UTR
		N = 664	N = 1288	N = 375	N = 658
Age	Mean (SD)	27.7 (8.9)	27.7 (8.1)	21.7 (5.5)	32.0 (9.8)
Gender	(% Male)	73	76	78	60
Highest education level	Primary school	18	12	2	1
	Special education	x	12	2	7
	Secondary school (low levels)	28	19	31	7
	High school	20	24	20	10
	Vocational education	18	17	21	19
	Vocational education (high)	8	9	8	17
	University	5	4	11	1
Marital status (%)	None	1	1	x	2
	Not married	90	82	–	42
	Married	5	9	–	14
	Divorced	4	3	–	1
Household (%)	Independent alone	38	31	–	x
	With parent(s)	34	36	–	39
	With partner/family	12	9	–	79
	Mental health institute	3	9	–	40
	Other	12	6	–	x
Primary diagnosis (%)	Schizophrenia	42	65	52	24
	Schizoaffective	5	11	10	2
	Schizophreniform	8	6	10	2
	Psychotic disorder	20	14	16	4
	Substance abuse	6	1	4	1
	Depression/bipolar	9	2	5	9
	Other	7	2	3	34
	Employed	45	53	58	31
Employment (%)	Unemployed	30	24	28	7
	Student	16	37	x	16
	Other	7	x	x	1
Antipsychotic (%)	None/not applicable	19	11	–	x
	Risperidone	29	18	–	4
	Olanzapine	28	22	–	10
	Quetiapine	4	5	–	3
	Clozapine	1	8	–	5
	Aripiprazol	2	6	–	2
	Strong DA-antagonist	16	10	–	3
PANSS total	Mean (SD)	56.7 (12.6)	56.7 (16.1)	65.5 (20.3)	48.0 (18.9)
PANSS Positive	Mean (SD)	12.6 (4.8)	12.6 (4.8)	16.2 (6.7)	11.8 (5.7)
PANSS Negative	Mean (SD)	14.3 (6.0)	14.3 (6.0)	16.0 (6.7)	12.1 (6.1)
PANSS General	Mean (SD)	29.7 (8.1)	30.0 (8.1)	33.3 (10.5)	24.3 (8.9)

et al., 2003; Fredrikson et al., 1997; Fresan et al., 2005; Higashima et al., 1998; Kawasaki et al., 1994; Kay and Sevy, 1990; Lancon et al., 1998, 1999, 2000; Lee et al., 2003; Lindenmayer et al., 1994a,b, Lindenmayer et al., 2004; Lindström and Von Knorring, 1993; Loas et al., 1997; Lykouras et al., 2000; Lépine et al., 1989; Mass et al., 2000; Rapado-Castro et al., 2010; Reichenberg et al., 2005; Van der Gaag et al., 2006a; Vilaplana et al., 2007; White et al., 1997; Wolthaus et al., 2000). See Supplementary material. PANSS items N5 Abstract thinking and N7 Stereotyped thinking from the original negative subscale of the PANSS, were seldom (both 3 times) reported as a negative symptom by these factor analyses and showed a correlation of <0.3 to the other negative symptoms, and were therefore not considered further in our analysis.

Further selection was based on correlations of N1, N2, N3, N4 or N6 with other PANSS items. A factor analysis requires items to have a moderate, positive inter-correlation (Stevens, 1996; Tabachnik and Fidell, 2007). A correlation matrix with Spearman's correlations of all items from the EPOG-database was created. Items showing a correlation of >0.3 for at least three times with N1, N2, N3, N4 or N6 were selected for further analysis. Based on the above criteria, the following were selected for factor analysis: N1 Flat

affect, N2 Emotional withdrawal, N3 Poor rapport, N4 Passive/apathetic social withdrawal, N6 Lack of spontaneity, G5 Mannerisms and posturing, G7 Motor retardation, G13 Avolition, and G16 Active social avoidance.

### 2.3. Exploratory factor analysis

Items selected according to the above criteria were entered into an EFA (Principal Axis Factoring) using Statistical Package for Social Sciences (SPSS 16). The factor analysis was based on the correlation matrix of the items. The Kaiser–Meyer–Oklin (KMO) and Bartlett's test for sphericity were calculated. The number of factors was not fixed beforehand, but factors were only retained when they showed an eigenvalue of >1. Items within a factor were only retained with a factor loading of >0.3. After factor estimation, both Direct Oblimin rotation with Kaiser Normalization and Varimax was applied. The Oblimin solution was reported because we expected the factors to be correlated ( $r > 0.32$ ) (Tabachnik and Fidell, 2007). The Varimax solution was reported for completeness, because Varimax is common practice in the field. Results can now be compared to other studies reporting the Varimax solution.



## 2.4. Confirmatory factor analysis

We then performed a CFA in LISREL 8 (Jöreskog and Sörbom, 2011) to investigate the fit of the model identified by EFA. Because of non-normality, an asymptotic covariance matrix was used for estimation and comparative fit indices were used instead of the traditional Chi-square values (Hu and Bentler, 1998; Lei and Lomax, 2005; Powel and Schafer, 2001; Yuan and Bentler, 1998). The factors identified by EFA were entered as latent variables in the CFA and the PANSS items were entered as observed variables. The maximum likelihood method was used for estimation (Van der Gaag et al., 2006a). We used multiple indices to measure goodness-of-fit: the Comparative Fit Index (CFI > 0.9), the Goodness-of-Fit index (GFI > 0.9), the Root Mean Square Error of Approximation (RMSEA < 0.06), the Root Mean Square of Residuals (RMR < 0.05), and an unstandardized factor loading >2 \* standardized factor loading (Albright and Park, 2009; Hu and Bentler, 1998; Marsch et al., 2004). Correlated measurement errors were introduced into the model based on significantly correlated residuals indicated by modification indices. Improvement of the model and the impact of correlated measurement errors were assessed in this way.

Many factor analyses on the PANSS focused on schizophrenia, while our focus was on psychotic disorders. To investigate whether this broader diagnostic inclusion of diagnoses compared to other studies affected the structure of symptoms, the CFA was repeated with patients with a DSM-IV diagnosis of schizophrenia from the GROUP database. Moreover, the severity of symptoms was relatively low, which may have an influence on the factor structure. Therefore, analysis was also repeated in 50% of the sample showing the highest summed score on the selected negative symptoms.

Correlated residuals were also introduced in both CFA models, similar to the model with all diagnoses and all cases included. The goodness-of-fit measures of both were compared to the original models, both with and without correlated residuals.

To test the validity of the factor structure, summed scores on both factors were non-parametrically correlated with neuropsychological and clinical measures of the GROUP database. We included the Community Assessment of Psychotic Experiences (CAPE; rating self-reports of lifetime psychotic experiences; Konings et al., 2006), Schedule for the Deficit Syndrome (SDS; categorizing patients into deficit or non-deficit subgroups; Kirkpatrick et al., 1989), Structured Interview for Schizotypy-Revised (SIS-R; semi-structured interview assessing schizotypal symptoms; Kendler et al., 1989; Vollema and Ormel, 2000), WAIS III (neuropsychological test; Wechsler, 1997), Camberwell Assessment scale of Need Short Appraisal Schedule (CANSAS; Slade et al., 1999), and the World Health Organization Quality of Life (Trompenaars et al., 2005). The SDS was of specific interest, as our factors may in some way be related to deficit syndrome. Qualitative (descriptive) differences in strength of non-parametric association between different PANSS factors were assessed.

## 3. Results

First, socio-demographic data of the cohorts were inspected and the EFA and CFA groups were compared (Table 1). The age of the subjects ranged mostly between 20 and 30 years, and 60–78% were male. Most subjects had a primary diagnosis of schizophrenia or a psychotic disorder. Around 10% of the subjects had another diagnosis, but these subjects had at least a differential diagnosis or comorbid diagnosis within the psychotic spectrum, which is not reported. Subjects from the Amsterdam cohort were generally younger and subjects from the Utrecht cohort had lower PANSS scores. All cohorts when tested separately showed a significant difference in age ( $p < 0.0005$ ), but the comparison between the EFA

and CFA samples did not ( $p = 0.20$ ). Gender ( $p = 1$ ) and diagnosis ( $p = 0.23$ ) were not significantly different between the EFA and CFA sample, whereas they were significantly different in the comparison between all four samples separately ( $p < 0.0005$ ). As the CFA sample was used in all analyses, non-significant differences in age, gender, and diagnosis between those two samples were considered most relevant for interpretation of the data. PANSS original subscales (Positive symptoms, Negative symptoms and General Pathology), defined by Kay et al. (1987) were significantly different between all samples (all  $p < 0.005$ ), but the differences were not regarded as clinically relevant (only one point difference in mean between samples).

## 3.1. Exploratory factor analysis

Inspection of a histogram of the data and a Q–Q plot showed a non-normal, left-skewed distribution. Factor analysis on EPOG ( $n = 644$ ) resulted in a Kaiser–Meyer–Oklin (KMO) of 0.85 (excellent) and a significant result for the Bartlett's test for sphericity ( $Chi = 2598.9$ ;  $p < 0.005$ ), indicating that the correlation matrix was suitable for factor analysis. A two-factor solution indicated an eigenvalue >1 (60% of the variance explained) with all factor loadings above 0.3. Communalities were all above 0.3, indicating that all items explained a substantial amount of variance. The two factors had a strong, negative correlation of  $-0.64$ , indicating the Oblimin solution should be reported ( $>0.32$ , according to Tabachnik and Fidell, 2007). The Varimax solution (Table 2) showed that, after rotation, items loaded preferably either on Factor 1 or Factor 2. The Oblimin rotation (Table 3) resulted in one factor with items loading the strongest in the positive direction, while Factor 2 items loaded the strongest in the negative direction.

## 3.2. Confirmatory factor analysis

The CFA was based on a merged sample of three databases (GROUP, Amsterdam, Utrecht) of 2172 cases. A model was created based on the results of the EFA (Fig. 1). The CFA by LISREL indicated a moderate fit if correlated residuals were not introduced into the model. The following goodness-of-fit indices were obtained (with criteria for a good fit given in brackets): CFI = 0.99 ( $>0.9$ ), GFI = 0.99 ( $>0.9$ ), RMSEA = 0.063 ( $<0.06$ ), RMR = 0.071 ( $<0.05$ ), and unstandardized factor loading/standardized factor loading >2 ( $>2$ ). Next, significantly correlated residuals (measurement errors) were introduced into the model to improve the fit (Cole et al., 2011; Gerbing and Anderson, 1984), see Fig. 1. This model resulted in the following fit: CFI = 1.0 ( $>0.9$ ), GFI = 1.0 ( $>0.9$ ), RMSEA = 0.015 ( $<0.06$ ), RMR = 0.015 ( $<0.05$ ), and unstandardized factor loading/

**Table 2**

Factor structure of factor analysis on items N1, N2, N3, N4, N6, G5, G7, G13 and G16 of the PANSS after Varimax rotation; Bold values indicate that the item loaded strongest on this factor.

	Factor 1		Factor 2	
	Unrotated loading	Rotated loading	Unrotated loading	Rotated loading
N6 Lack of spontaneity	<b>0.756</b>	<b>0.807</b>	0.357	0.202
N3 Poor rapport	<b>0.744</b>	<b>0.759</b>	0.297	0.257
N1 Flat affect	<b>0.713</b>	<b>0.594</b>	0.080	0.403
G7 Motor retardation	<b>0.645</b>	<b>0.571</b>	0.124	0.325
G5 Mannerisms and posturing	<b>0.443</b>	<b>0.460</b>	0.189	0.144
G13 Avolition	<b>0.435</b>	<b>0.406</b>	0.117	0.194
N4 Passive/apathetic social withdrawal	0.807	0.287	<b>−0.503</b>	<b>0.906</b>
N2 Emotional withdrawal	0.777	0.386	<b>−0.315</b>	<b>0.744</b>
G16 Active social avoidance	0.431	0.158	<b>−0.261</b>	<b>0.478</b>

**Table 3**

Factor structure of factor analysis on items N1, N2, N3, N4, N6, G5, G7, G13 and G16 of the PANSS after Oblimin rotation; the unrotated solutions are identical to the unrotated Varimax solution; Bold values indicate that the item loaded strongest on this factor.

	Factor 1		Factor 2	
	Pattern coefficient	Structure coefficient	Pattern coefficient	Structure coefficient
N6 Lack of spontaneity	<b>0.896</b>	<b>0.833</b>	0.099	−0.472
N3 Poor rapport	<b>0.822</b>	<b>0.801</b>	0.033	−0.491
N1 Flat affect	<b>0.577</b>	<b>0.697</b>	−0.219	−0.575
G7 Motor retardation	<b>0.563</b>	<b>0.649</b>	−0.135	−0.494
G5 Mannerisms and posturing	<b>0.503</b>	<b>0.481</b>	0.034	−0.286
G13 Avolition	<b>0.416</b>	<b>0.449</b>	−0.510	−0.316
N4 Passive/apathetic social withdrawal	−0.033	0.586	<b>−0.971</b>	<b>−0.950</b>
N2 Emotional withdrawal	0.158	0.623	<b>−0.729</b>	<b>−0.830</b>
G16 Active social avoidance	−0.10	0.315	<b>−0.510</b>	<b>−0.504</b>

standardized factor loading  $> 2$  ( $> 2$ ). These indices indicate a good fit of the model when correlated residuals were introduced.

The CFA was repeated in a sample of 845 cases with a DSM-IV diagnosis of schizophrenia from the GROUP database. The following goodness-of-fit indices were obtained in the model without introduced correlated residuals: CFI = 0.98, GFI = 0.99, RMSEA = 0.070, RMR = 0.079. In the model with correlated residuals the following values were obtained: CFI = 1.0, GFI = 1.0, RMSEA = 0.0082, RMR = 0.019. Analysis on 50% of the sample with the highest summed negative symptoms gave the following model fits without correlated residuals: CFI = 0.95, GFI = 0.98, RMSEA = 0.087, RMR = 0.062. With correlated residuals the following fits were obtained: CFI = 0.98, GFI = 0.99, RMSEA = 0.052, RMR = 0.038. The CFA analyses with the schizophrenia group showed similar results to the analyses on the whole sample, both with and without correlated residuals. The analysis on symptom severity showed marginally higher values, but still within the thresholds indicating a good model fit.

Both factors showed a moderate to strong correlation with the SDS. Interestingly, we observed a stronger correlation of the non-social items with our Factor 1, and a stronger association between social SDS items and Factor 2. With lower correlations, a similar pattern was observed for the CANSAS. The CAPE and SIS-R showed

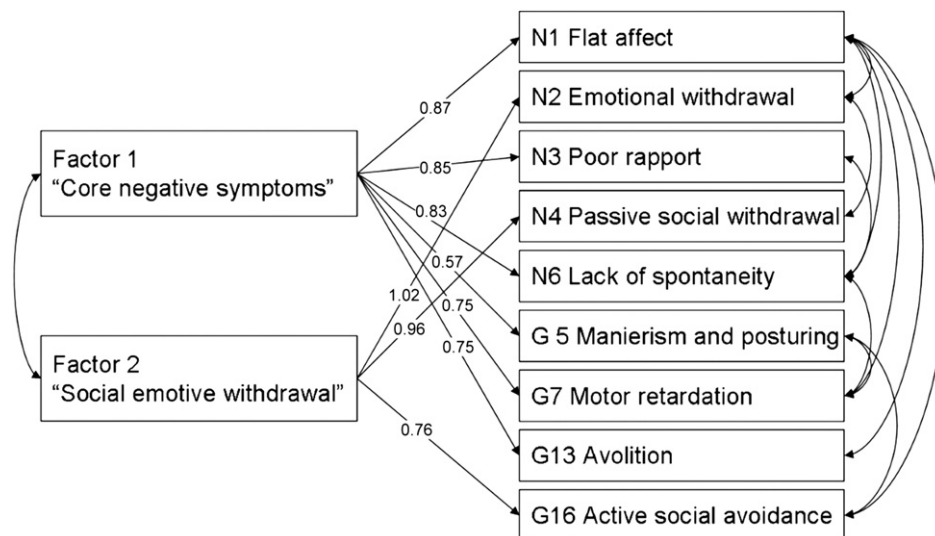
small to moderate correlations with both factors (0.1–0.4), but always slightly stronger for Factor 2. The WAIS showed a negative correlation with both factors, but now minutely stronger with Factor 1. Quality of life (QoL) was also lower for patients with higher scores of both factors, but the effect of Factor 2 was stronger.

#### 4. Discussion

We found that a two-factor model represents negative symptoms better than a single factor, albeit that the two factors are correlated. We confirmed this two-factor model by CFA in a separate cohort and demonstrated that the model is not restricted to a diagnosis of schizophrenia or to higher symptom severity, but also fits for psychotic disorders with milder levels of symptoms. The first factor of the model comprises items that show similarity to the “expressive deficits” domain of DSM-V, with the highest factor loadings on Flat affect (N1), Poor rapport (N3), and Lack of spontaneity (N6). In the second factor, the items resembled aspects of the “social amotivation” domain of DSM-V, with the highest loadings on Emotional withdrawal (N2) and Passive/apathetic social withdrawal (N4).

Our two-dimension structure of negative symptoms provided good support for the two negative symptom domains proposed in the DSM-V (Messinger et al., 2011) and agrees with earlier proposed symptom models (Keefe et al., 1992; Kirkpatrick et al., 2001). Moreover, the two-factor division determined by PANSS robustly extends the results of other studies suggesting two negative symptom domains that were mainly based on SANS (Bell et al., 2011; Blanchard and Cohen, 2006; Foussias and Remington, 2010; Keefe et al., 1992; Kimhy et al., 2006; Kirkpatrick and Fischer, 2006; Lindström and Von Knorring, 1993; Messinger et al., 2011; Peralta and Cuesta, 1995; Van den Oord et al., 2006).

Of note, Avolition (G13) and Flat affect (N1) would conceptually also fit Factor 2, social avolition/amotivation. Indeed, the items loaded relatively strong on both factors. We removed both items from the EFA separately to investigate the effects on factor structure. But as this did not change the factor structure of the other items, we retained both items in the model. Factor analysis is a data-driven method, and multiple aspects may influence the factor loading of items. While Flat Affect (N1) and Avolition (G13)



**Fig. 1.** The factor model created for the confirmatory factor analysis (CFA) based on the results of the exploratory factor analysis (EFA). The two boxes on the left indicate our factors, the boxes on the right indicate the PANSS items connected to their corresponding factor by arrows, and the arrows connecting the right-hand boxes indicate the correlated residuals introduced into the model. Values on top of the arrows indicate the factor loadings. Each item also has its own error term, but these are not shown for simplicity.

measure social communicative deficits and amotivation, the rating of these PANSS items is merely based on observed behavior. Therefore, the items may be rated as disturbance in willful initiation of behavior or facial expression, and also load the “expressive behavior factor”.

For the negative symptom model as identified in our study, the CFA showed a low loading or poor fit of PANSS item Mannerisms and posturing (G5). Possibly because this item in general does not receive a high score in ratings and provides a limited amount of variance. But as excluding it did not improve the CFA fit and the item showed a loading of  $>0.4$  in the EFA, we retained the item in the model. In the DSM-V, this item would probably fit better in the abnormal psychomotor behavior. In addition, the Motor retardation (G7) and Avolition (G13) items also loaded lower on Factor 1, possibly because they originate from the General Pathology sub-scale of the PANSS.

The fit of the CFA improved when we added a correction for measurement errors to the model. An explanation could be that, although the interviewers were well-trained, some PANSS items may have a common origin that is difficult to disentangle and thus rated in multiple items (Cole et al., 2007; Gerbing and Anderson, 1984), e.g. reduced movement could be rated as Flat affect (N1), Mannerism and posturing (G5), or Motor retardation (G7).

Some authors have speculated that the “expressive deficits” factor may reflect directly apparent symptoms that change quickly over time, while the “social amotivation” factor reflects the status of social relationships that may change more slowly (Blanchard and Cohen, 2006; Foussias and Remington, 2010; Keefe et al., 1992). Moreover, the first group of symptoms is rated as directly observed behavior, while the social items are based on reports from family members and nursing staff (Messinger et al., 2011). Indeed, directly observed behavior – Poor rapport and Lack of spontaneity – show the highest loading on Factor 1 and thus have the strongest impact in this factor.

“Social amotivation” may be due to a diminished capacity of patients to anticipate pleasurable events, despite intact hedonic consumption (Foussias and Remington, 2010; Oorschot et al., 2011). This explanation finds support in the strong loading of emotional and apathetic withdrawal. Moreover, the “social amotivation factor” could, besides interest, also include aspects of social performance, based on engagement in social situations (Keefe et al., 1992; Oorschot et al., 2011).

When correlating our factor structure with clinical and psychological measures, we observed a subtle but very stable difference in correlations of both factors with other measures. The results suggested that both factors relate equally to deficit syndrome, but that “Expressive deficits” relate stronger to non-social items, and “Social amotivation” to social items. A similar structure of a social and non-social symptom group in the SDS has been reported previously (Kimy et al., 2006).

Moreover, “Expressive deficits” had a stronger association with neuropsychological function, while “Social amotivation” had a stronger association with self-reported symptoms and quality of life. In the past, a distinction has also been made between neuro-cognition and social cognition. Possibly, the “Expressive deficits” factor is more closely related to neurocognitive impairments, while social cognition and the “Social amotivation” constitute a separate domain (Bell et al., 2011; Foussias and Remington, 2010). Furthermore, social function may relate more strongly to quality of life than other negative symptoms captured in our Factor 1, as shown previously (Bell et al., 2011).

On a different note, Marder et al. (1997) showed in an EFA that factor loadings on all three items of our Factor 2 had the largest differential effect in response to haloperidol versus risperidone treatment. Van Oord et al. (2006) found a similar distinction in negative symptom structure as we do, and concluded that current

use of atypical medication could make the two factors can be discerned now, whereas (high dosage) classic antipsychotics in the past may have obscured the two subdomains.

Negative symptoms and depressive symptoms are often considered to be associated (Fitzgerald et al., 2002; Lako et al., 2012). Additional analysis in this study showed no association between depression and negative symptoms (results not shown), while previous factor analyses also showed no loading of Depression (G6) on the negative symptom factors. Thus, the “expressive deficits” factor may be more a reflection of apathy than of depression. Research using scales specifically designed for assessing apathy (Clarke et al., 2011) or depression (Lako et al., 2012) could further corroborate this.

A unique strength of our study is its large sample size and its replication in large, independent cohorts. CFA is a complicated procedure and depends strongly on the underlying data structure (Van der Gaag et al., 2006a), thus our confirmation of the negative symptom structure can be considered quite robust. In addition, this study is the first to replicate findings of studies on the SANS by using the PANSS. This is a useful addition, as the PANSS is more frequently used in research settings and clinical practice, and it also covers a broader range of symptoms (Fitzgerald et al., 2001; Van den Oord et al., 2006). Of note, we reported both Varimax and Oblimin rotation solutions. Whereas Oblimin is more valid given the correlation between both factors, Varimax is often used and therefore reported to enable comparison with other studies.

Some limitations should also be mentioned. The two-factor structure may be an artifact, because the first factor includes symptoms rated by the interviewer during the interview, while the second factor includes social activities outside the interview room (Blanchard and Cohen, 2006). In this study, patients were relatively young and often in the early stages of their illness, with only 25% suffering from more severe negative symptoms (PANSS items  $> 3$ ). This limits our ability to draw conclusions about symptom dimensions in, for example, chronically ill samples. Lastly, the two factors show a considerable association with each other and may partly overlap. But because of the extensive support from earlier findings, the two factors have good construct validity.

In conclusion, our results support the two subdomains proposed in the DSM-V. The first subdomain is related to the “expressive deficits”, while the second could be described as a “social amotivation” factor. Negative symptoms are difficult to treat and the pathophysiology remains poorly understood. By acknowledging the two dimensions that have now emerged robustly from the factor structure of systematic assessments, the effects of interventions may be assessed with greater precision (Kirkpatrick and Fischer, 2006; Blanchard and Cohen, 2006). Research into their differential pathophysiology, e.g. using neuroimaging, could advance our understanding of these debilitating symptoms further (Bell et al., 2011).

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## Contributors

Edith Liemburg undertook part of the statistical analysis and wrote the manuscript.



Stynke Castelein undertook part of the statistical analysis and wrote the manuscript.

Roy Stewart performed part of the statistical analysis.

Mark van der Gaag provided background and detailed advice about the study.

André Aleman provided background on content of the study.

Henderikus Knegtering designed the study.

Genetic Risk and Outcome of Psychosis (GROUP) Investigators provided data for analysis in the study and revised the manuscript.

All authors contributed to and have approved the final manuscript.

## Disclosures

The Authors have declared that there are no conflicts of interest in relation to the subject of this study.

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## Appendix A

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## Appendix B. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.jpsychires.2013.01.024>.

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